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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/557,586	03/03/2006	Maria Assunta Costa	1136-PCT-US	8745

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/557,586	COSTA ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on 05/27/2010 is acknowledged.

2. Claims 29-33 are pending are under consideration as they read on a multimer protein molecule comprising amino acid sequences SEQ ID NO:4 and SEQ ID NO:2.

3. In view of Applicant's response on 05/27/2010 only the following rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 29-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Columbo et (Reference 7; IDS file 11/17/2005) in view of Pauli et al. (PTO-892 mailed on 12/28/2009; Reference U) for the same reasons as set forth in the Office Action mailed on 12/28/2009.

Applicant's arguments filed on 05/27/2010 have been fully considered, but arenot found persuasive.

Applicant argues:

Applicants submit that Columbo et al. only focuses on Parj 1 and the identification of putative IgE binding regions. In particular, Colombo et al. describe the IgE binding activity of a portion of the Par j I allergen (i.e. the region 1-30). In this context, Colombo et al. teach:

- that the cysteines in position 14 and 29 are essential for IgE binding *(see* Colombo et al., paragraph epitope mapping" from p. 2781 to p. 2782); and that single mutation K21, K23, E24 or K27 causes loss of binding *(see* p. 2782, left column, second paragraph, Fig. 3A and 3B.

Applicants submit that Columbo et al. do not report the effect of a single mutation (K21, or K23 or E24 or K27) on the full length Parj i; do not report the effect of more than one mutation on the 30 amino acids derived Parj 1 molecule or on the full length Parj 1 molecule; and do not report any data on Parj 2 and its mutations.

Regarding Pauli et al, Applicants submit that Pauli indicates in the introduction at p. 1077, left column, first sentence that there are two birch pollen allergens, Bet vl and Bet v2. Pauli et al., however, only describe the allergenic activity of birch pollen allergen Bet vl. Pauli teaches oligomers (dimer and trimer) of Bet vl that are produced by ligation of two or three copies of the Betvl cDNA in a plasmid followed by expression in *E. coli (see* Pauli at p. 1077, left column, third paragraph).

The homodimer (Betvl-Betvl) and homotrimer (Betvl-Betvl-Betvl) are shown to induce no reaction at a concentration of i0 ug/ml in the prick test *(see* Pauli at p. 1079, left column, first paragraph and Fig. 2). In addition, the Betvl homotrimer seems hypoallergenic after intradermal testing of birch allergic patients *(see* Fig. 3b and Fig. 4a). Pauli indicates at p. 1081, right column, last sentence to p. 1082, left column, first sentence that: *"one has to consider that the absence of local reactions during intradermal testing cannot predict the absence of systemic effects during immunotherapy"*.

Thus, Applicants submit that that the teachings of Pauli are strictly limited to multimers of the same molecule and to Betvl allergens. Pauli et al. do not teach any other strategy of cloning.

In contrast, the molecules of the present invention comprise a combination of a full length Parj 1 mutated in three specific positions, namely K23, E24 and K27, and a full length Parj 2 mutated in three specific positions, namely K23, E24 and K27.

The combination of Columbo et al. and Pauli et al.

Columbo relates only to single mutants of the 1-30 portion Par j i. Based on the teaching of Columbo, cysteines replacement by serine at position 14 and 29 as well as mutation of the single residues K21, K23, E24 or K27 in a Parj 1 derived molecule of 30 amino acids would decrease or cause loss of IgE binding.

Therefore, starting from Columbo et al. with the aim of producing a potential agent to reduce allergenic response to Par j i, the skilled in the art would produce a molecule of 30 amino acids (see Fig. 3A) having mutated cysteines in position 14 or 29 or molecules of 30 amino acids having the single mutation K21, K23, E24 or K27. Columbo et al. do not teach or provide any data to show a molecule comprising full length Parj 1 in which three specific residues, namely K23, E24 and K27, are mutated. Let alone that such molecule could have hypoallergenic properties.

The combination of Columbo and Pauli would not lead to the molecules of the present invention because Pauli et al. only teach multimers of the same molecule. There is absolutely no suggestion in Colombo to combine Par j 1 and Par j 2 to create an hypoallergenic molecule. Colombo does not show any data on Par j 2 mutants; nor does Colombo indicate or suggest that

> mutations of the corresponding single residues K21, K23, E24 or K27 in a Parj 2 derived molecule of 30 amino acids would decrease or cause loss of IgE binding."
>
> "As another line of evidence, Applicants would like to indicate that a paper by Costa et al. *(see* Exhibit A) demonstrated that the Parj2 allergen contains at least four independent IgE epitopes. Disruption of one epitope does not necessarily exclude the possibility that the remaining IgE epitopes will not trigger the target cells (as shown in Costa et. al., Allergy (2OOO)).
>
> Accordingly, Applicants submit that the present invention of making a molecule possessing hypoallergenic properties by merging two independent allergens (Parjl + Parj2), each of which is mutated in just one IgE epitope, is not obvious in view of prior publication such as Costa et al."

It remains the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Columbo et al. and Pauli et al. produce a multimer protein comprising Par j 1 and Par j 2 to treat allergies because Par j 1 and Par j 2 are the major allergens of Parietaria pollen. It would have been obvious to only include these two allergens since they are the two major allergens and it is desirable to produce pharmaceutical compositions which only comprise the most important allergens without the confounding effects of the seven minor allergens and other components normally present in pollen allergen extracts. By combining Par j 1 and Par j 2 into a single molecule, the molar ratio of the two allergens will be constant, thus providing a controlled dosage of both allergens to patients for optimal immunotherapy use. Because Pauli et al. teaches that dimerization and trimerization of allergens does not lead to a change in the conformation of the allergen fold and Columbo et al. teaches that the 1-30 IgE epitope of Par j1 and Par j 2 is a conformational, discontinuous epitope, it would also have been obvious to perform mutational analysis at the positions taught by Columbo et al. to generate a Par j1/ Par j2 multimer protein with reduced IgE binding at that epitope. One would be motivated to do this because Columbo et al teaches that it is an important IgE epitope and because the multimer is being generated for in vivo use. It is

obvious to combine two compositions which are known to have the same use. One of ordinary skill in the art at the time of invention would have been motivated to perform mutations to arrive at SEQ ID NOs 2 and 4 and to combine these sequences into a multimer for in vivo allergy therapy use, which may further contain an adjuvant because such a molecule would be expected to exhibit reduced IgE binding in addition to reduced effector cell activation when used in vivo to treat allergies. It would be obvious to one of ordinary skill in the art at the time the invention was made to combine the compositions of Columbo et al. and Pauli et al. because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Pauli et al. need not teach multimers of Parietaria allergens, nor do the references need to teach the resulting multimers. The references, when taken together, supply the motivation to be combined to result in the claimed invention. As such, the rejection is maintained for reasons of record.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 2, 2010

/Nora M Rooney/

Primary Examiner, Art Unit 1644